



Case Report

Recurrence of Takotsubo cardiomyopathy with coronary slow flow phenomenon

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Summary This report presents the case of a 54-year-old female with Takotsubo cardiomyopathy that recurred 12 years after the first episode. The coronary angiography at the first admission revealed ergonovine-induced coronary vasoconstriction in the left coronary artery, and recurrence recurred after the interruption of vasodilator therapy to prevent vasospasm. In addition, the coronary angiography both in the first and second event demonstrated coronary slow flow phenomenon, which improved after the intracoronary administration of nicorandil. These findings indicate that coronary microvascular constriction plays an important role in the pathophysiology of Takotsubo cardiomyopathy.

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Introduction

Takotsubo cardiomyopathy [1], which is also referred to as either apical ballooning or stress cardiomyopathy, is characterized by the sudden onset of chest symptoms, electrocardiographic changes consistent with myocardial ischemia, and reversible left ventricular dysfunction without substantial coronary stenosis. Although the precise etiologic basis of this syndrome remains unclear, several pathophysiological mechanisms have been proposed, such as acute multivessel coronary vasospasm, endothelial

functional abnormality, microvascular dysfunction, and catecholamine-mediated cardiotoxicity [2–5].

Microvascular constriction is thought to be the main determinant of left ventricular wall motion abnormalities in the syndrome; however, whether microvascular dysfunction is the primary cause of the syndrome or an only secondary phenomenon remains unclear. This report presents a case of recurrent Takotsubo cardiomyopathy with coronary slow flow phenomenon (CSFP) after an interruption of vasodilator treatment, which suggests that microvascular spasm may thus play an important role in this syndrome.

Case report

A 54-year-old female taking betamethasone 0.5 mg/day for polymyalgia rheumatica was referred in 1997 because of sudden chest pain. The chest pain had been relieved shortly

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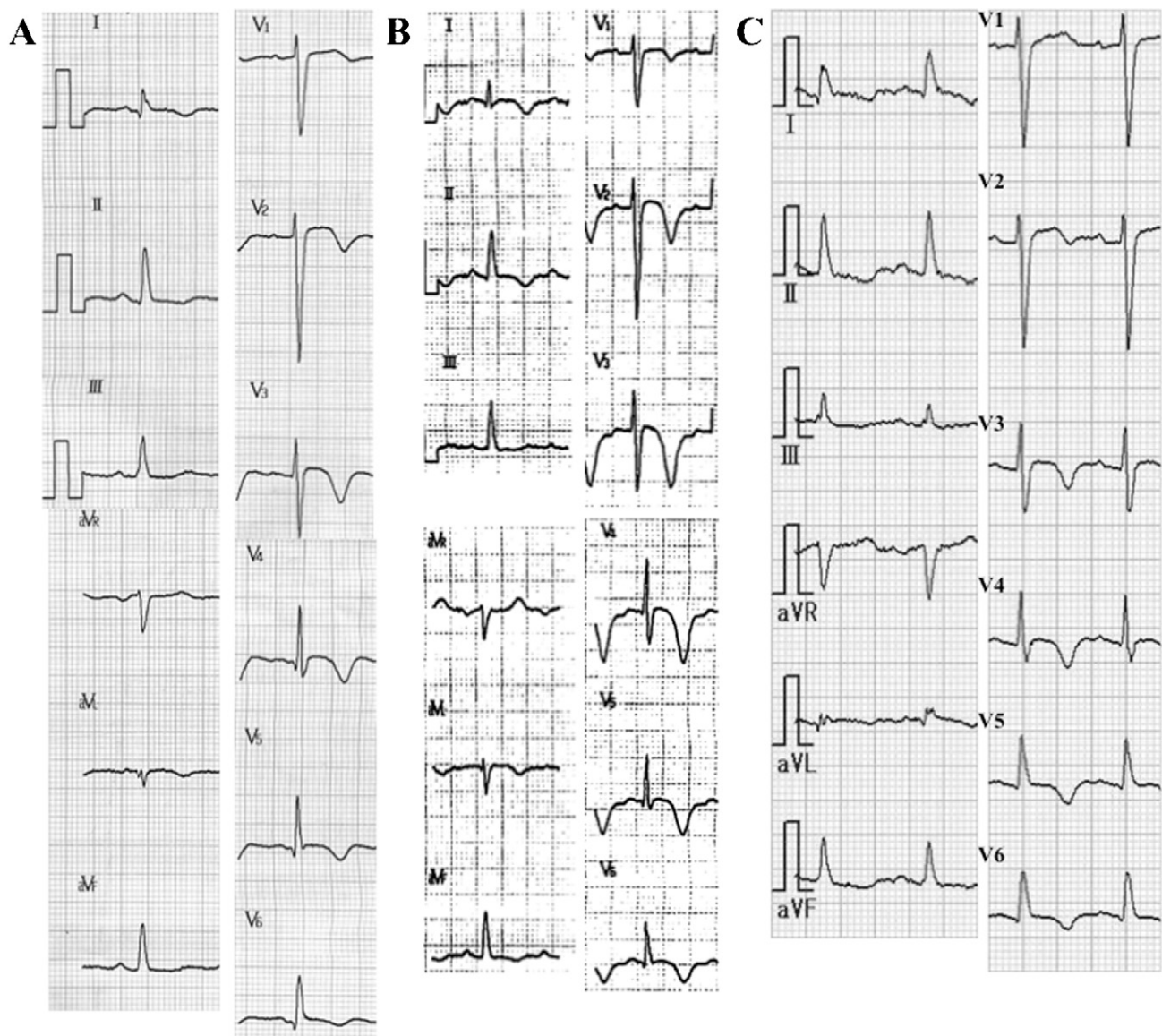


Figure 1 The electrocardiogram (A) on the first admission showed mild ST elevation with inverted T wave in the anterolateral leads, and the T wave inversions became deeper on the 3rd day (B). The electrocardiogram on the second admission (C) was similar to that on the first admission.

after admission; however, her electrocardiogram showed a mild ST elevation in the anterolateral leads with inverted T wave (Fig. 1A) and the echocardiogram demonstrated left ventricular apical ballooning. These findings led to the decision to perform emergency cardiac catheterization, which revealed left ventricular apical ballooning (Fig. 2) and no organic coronary stenosis (Fig. 3A). However, the coronary flow was delayed (Fig. 3B) and Table 1 shows the corrected Thrombolysis In Myocardial Infarction (TIMI) frame counts, which was adjusted to 30 frames/s and divided by 1.7 for the left anterior descending artery [6]. Her blood pressure was 140/80 mmHg, and her heart rate was 82/min. Her electrocardiogram transiently showed deep negative T waves (Fig. 1B) and the apical ballooning was gradually normalized in 2 weeks. Elective cardiac catheterization was performed on the 18th day. The left ventriculogram was almost normal and coronary angiography revealed ergonovine-induced

diffuse constriction of the left coronary artery (Fig. 3C). The coronary flow initially improved in comparison to that at the time of admission; however, the coronary flow was delayed after the spasm provocation test followed by the intracoronary administration of isosorbide dinitrate (Fig. 3D; Table 1). Biopsy samples from the right ventricle showed mild interstitial myocardial fibrosis and edema (Fig. 4). These findings indicated that coronary microvascular spasm caused the reversible apical ballooning in this case, although the role of the epicardial spasm was unclear, and thus diltiazem and isosorbide dinitrate were prescribed to prevent vasospasm.

The medications prevented her from experiencing a heart attack for 12 years after the event, while a diagnosis of dyslipidemia led to the administration of pravastatin. One of her relatives died in 2009, and her medication was interrupted. She was transferred to the hospital because

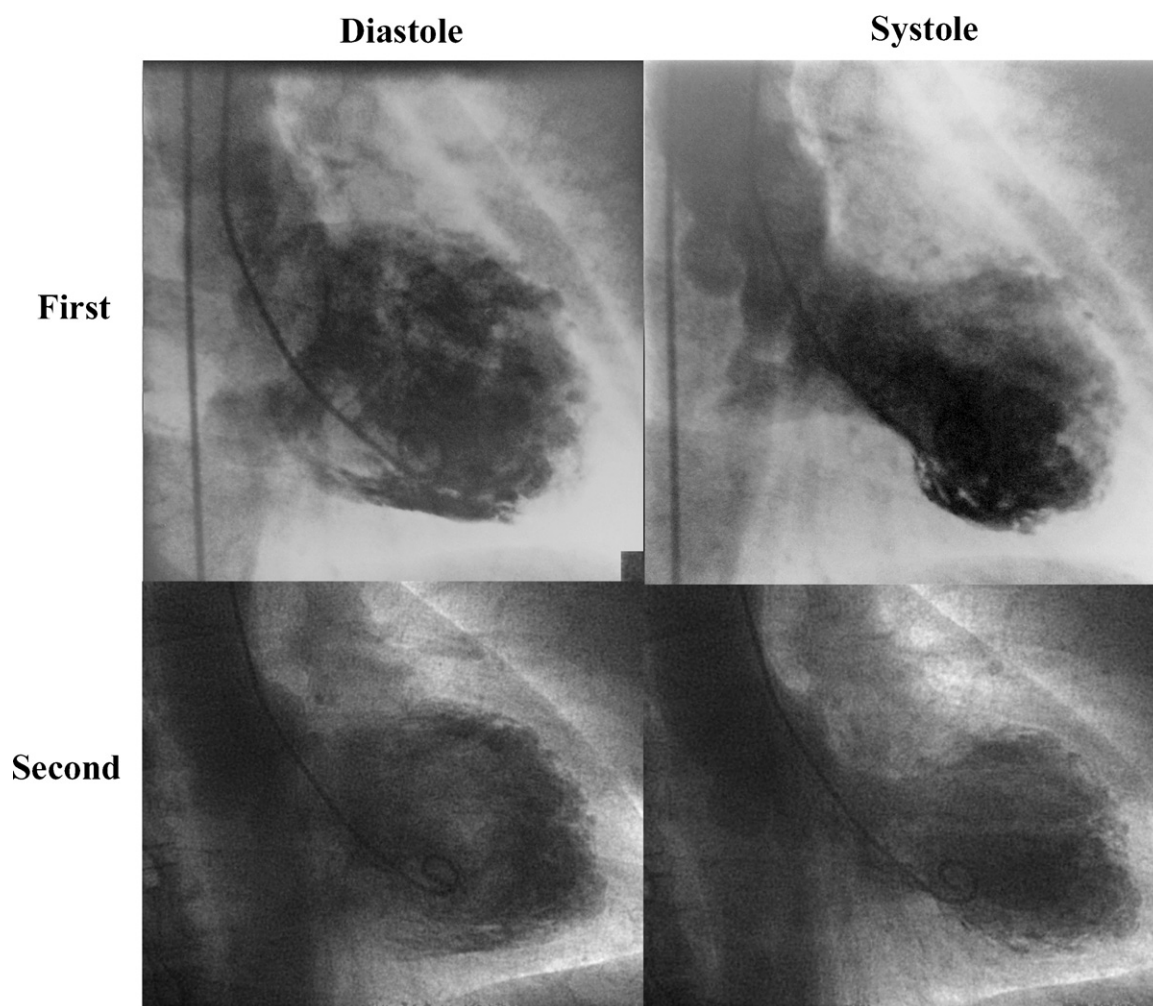


Figure 2 Left ventriculography both at the first emergency cardiac catheterization (First) and at the second admission (Second) showed similar shaped apical ballooning.

of a second heart attack a few days later. Her chest pain continued and the physical examination findings were unremarkable. Her blood pressure and heart rate were 126/84 mmHg and 94 beats/min, respectively. The white blood cell count increased to $9.0 \times 10^9/L$, while the heart-type fatty acid-binding protein and creatine kinase were not

elevated. Chest X-rays did not show pulmonary congestion, cardiomegaly, or aortectasis, and her electrocardiogram revealed a mild ST elevation with negative T wave in the anterolateral leads, which was similar to that at the first admission (Fig. 1C). The echocardiogram demonstrated mid to apical segment akinesis, which was also similar to the apical ballooning observed in 1997. Emergency coronary angiography showed no organic stenosis, thrombus, or epicardial spasm; however, the coronary artery flow was severely delayed (Table 1; Fig. 5A). Although the administration of isosorbide dinitrate did not change the slow flow, the intracoronary injection of nicorandil 2 mg improved the delayed flow (Fig. 5B, Table 1). In addition, the nicorandil relieved her chest oppression. Left ventriculography showed apical ballooning with a decreased ejection fraction of 46% (Fig. 2). Her hemodynamics remained stable during the intracoronary administration, and her blood pressure and heart rate at the start and the end of the cardiac catheterization were 120/90 mmHg and 122/77 mmHg, and 93/min and 93/min, respectively. The oral administration of diltiazem and nicorandil were started immediately to prevent coronary spasm. The creatine kinase remained within the normal range. The apical ballooning improved

Table 1 Corrected Thrombolysis In Myocardial Infarction frame counts of coronary angiography.

	LAD	LCX	RCA
First admission			
Emergency	45	37	81
Control	31	27	34
After spasm provocation	41	32	63
Second admission			
Control	62	58	140
Isosorbide dinitrate	61	56	ND
Nicorandil	33	34	ND

LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; ND, not done.

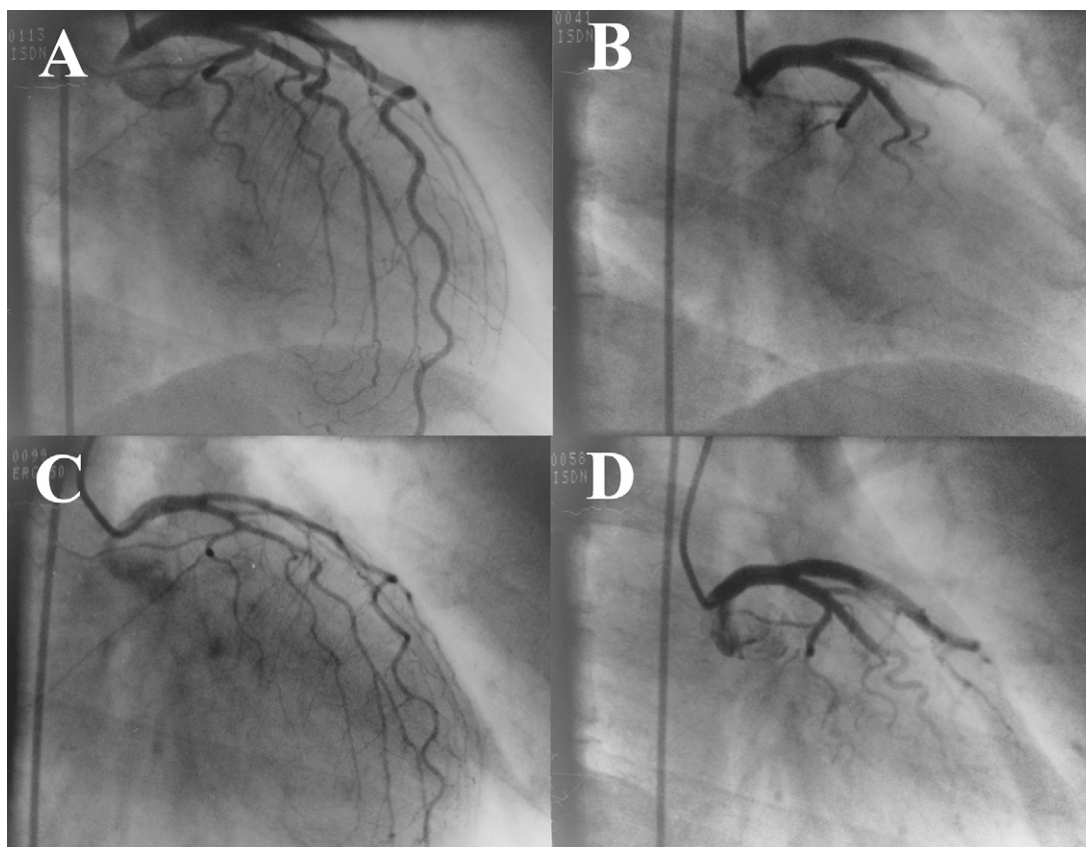


Figure 3 Coronary angiography at the first admission. Emergent coronary angiography demonstrated no organic coronary stenosis in the left coronary artery (A) and the right coronary artery. However, the coronary flow was delayed and the left coronary artery was not filled to the distal at the 20th frame (B), which was acquired at 30 frames/s. Elective angiography before the discharge revealed ergonovine-induced diffuse constriction in the left coronary artery (C). The coronary flow was delayed after the intracoronary administration of isosorbide dinitrate, and the distal portion of the left coronary artery was not filled with the contrast at the 20th frame (D).

within 3 days and the ejection fraction increased to 57%. The negative T waves in her electrocardiogram became deeper in 1 week and then gradually normalized within 2 months.

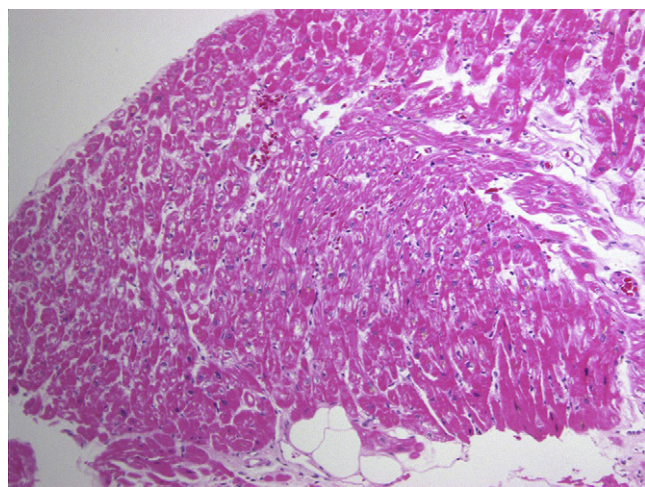


Figure 4 A biopsy sample from the right ventricle showed mild interstitial myocardial fibrosis and edema without contraction band necrosis.

Discussion

CSFP is an angiographic finding characterized by a delayed progression of contrast medium in an epicardial coronary artery without significant coronary stenosis. This phenomenon with chest pain was first reported in 1972 [7]. The overall incidence of CSFP is 0.9% among patients undergoing coronary angiography [8], and 7–24% in patients with normal coronary angiograms presenting with angina-like chest pain [9,10]. This phenomenon is observed in 35% of patients with suspected acute coronary syndrome [11]. CSFP is typically found in young male smokers and the long-term outcome is unclear. However, the rate of clinical recurrence is 84% [12], and a case of serious arrhythmia and sudden cardiac death has been reported [13]. Several mechanisms have been proposed for CSFP [14], and although the pathophysiology may be heterogeneous, intense vasoconstriction of resistant coronary arteries is thought to represent the major mechanism of angina in patients with CSFP [15].

The coronary flow is prolonged in almost all patients with Takotsubo cardiomyopathy, and their TIMI frame counts increase significantly in all 3 major coronary arteries in Japan [16], and also in Western countries [17–19]. This finding is consistent with a reduced coronary flow reserve

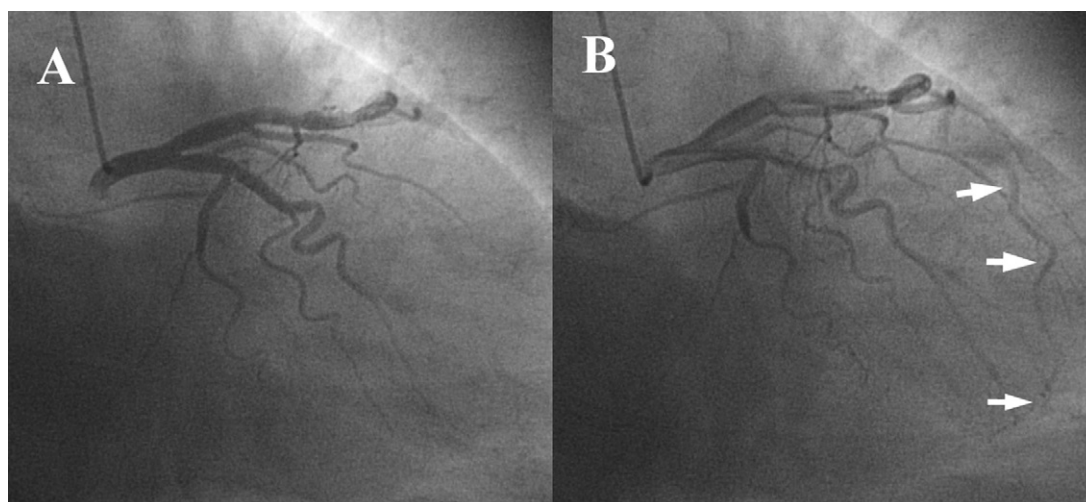


Figure 5 Emergent coronary angiography at the recurrence. Control angiography showed severely delayed coronary flow and the distal portion of left coronary artery was not visualized at the 20th frame (A), which was acquired at 15 frames/s. The distal left anterior descending artery (arrows) was filled with the contrast at the 20th frame after the intracoronary administration of nicorandil (B).

[20–22] and abnormal myocardial perfusion [4]. Myocardial contrast echocardiography demonstrated that the regional wall motion abnormality and the perfusion defect in the acute phase temporarily decrease with intravenous infusion of adenosine, promptly returning to baseline immediately after cessation of the adenosine [23]. In addition, another report showed an elevated index of microcirculatory resistance measured using a coronary pressure wire [24]. Therefore, the contribution of coronary microvascular constriction in the pathophysiology of Takotsubo cardiomyopathy seems to be obvious. On the other hand, a recent study demonstrated that intracoronary administration of nicorandil improved the prolonged frame count in patients with CSFP [8]. Nicorandil is a hybrid molecule containing an ATP-sensitive potassium channel opener and a nitric oxide donor, and it behaves as a selective dilator of resistance vessels [25]. The improvement in CSFP suggested that the presence of spasm in resistance vessels is the main factor in the pathogenesis of the CSFP. The similar improvement of the increased TIMI frame count with nicorandil in the present case supported the contribution of coronary microvascular spasm also in Takotsubo cardiomyopathy.

Ergonovine-induced coronary vasoconstriction in the left coronary artery and the recurrence of Takotsubo cardiomyopathy after the interruption of isosorbide dinitrate and a calcium-channel blocker treatment might therefore indicate that coronary spasm plays an important role in recurrence. Multivessel epicardial coronary spasm is one of the proposed mechanisms of Takotsubo cardiomyopathy [26]; however, the absence of spastic occlusion in the epicardial coronary artery during ST elevation does not favor that hypothesis. In addition, the 1.6–11.4% rate of recurrence of Takotsubo cardiomyopathy [27–31] is relatively small in comparison to that of spastic angina [32,33]. Moreover, a chronobiological analysis of Takotsubo cardiomyopathy shows a lower frequency of onset at night, whereas epicardial spasm most often occurs from midnight to early morning [34–36]. The low recurrence rate and the different circadian variations

also indicate the low probability of epicardial coronary spasm as the mechanism of Takotsubo cardiomyopathy. On the other hand, the clinical implications of epicardial coronary vasoconstriction, which was provoked in the present patient, have not yet been fully elucidated, but are related to epicardial spasm and microvascular dysfunction [37,38]. Moreover, Sun et al. demonstrated that coronary microvascular spasm contributed to myocardial ischemia in patients with epicardial coronary spasm [39]. Therefore, hyperreactivity in the epicardial coronary artery and that in the microvessel can be coincident in some patients, and the pathophysiology may be identical.

It remains unclear whether microvascular spasm in the present patient was the primary cause of Takotsubo cardiomyopathy and the vasodilator therapy prevented a heart attack, or a secondary phenomenon to catecholamine excess. The patient had not suffered from chest pain except for the two attacks, and the administration of nicorandil improved chest pain and coronary slow flow, and thus the microvascular dysfunction may be transient. She had experienced emotional stress prior to the second attack, which was a typical onset pattern of Takotsubo cardiomyopathy. Therefore, catecholamine-induced myocardial toxicity was a possible pathogenic mechanism underlying the microvascular spasm, although the serum catecholamine levels were not measured in this patient. However, the patient's normal blood pressure and heart rate at the admission and the lack of findings of contraction band necrosis in the biopsied myocardium might imply that catecholamine has only a minor role in the pathophysiology of the disease.

There is no consensus concerning the chronic management of Takotsubo cardiomyopathy. Although the abnormal catecholamine dynamics related to emotional distress indicate that a beta-adrenoreceptor blockade might prevent the recurrence of Takotsubo cardiomyopathy, several reports have so far failed to show any preventive effect of prior chronic treatment with beta-blockers [29,30,40], and beta-blockers might even worsen the condition [27]. This failure

of beta-blockers to prevent coronary microvascular spasm might make sense, and vasodilators of coronary microcirculation, like calcium-channel blockers and nicorandil, may therefore be potential therapeutic agents to investigate in future trials. The potentiality of the vasodilators is also supported by the recurrence after the withdrawal of a calcium-channel blocker and the improvement of coronary slow flow by the administration of nicorandil in the present case.

Takotsubo cardiomyopathy was first described in Japan, and this condition was widely recognized. Long-term follow-up data are still lacking, and thus the recurrence with a similar pattern 12 years after the first episode is a rare case. More recurrent cases will be collected within the next decade, and comparison between the episodes and assessment of medications could therefore be a key to better understand the pathophysiology of this disease.

Conclusions

This report presented a case of Takotsubo cardiomyopathy, in which the interruption of vasodilator therapy may have led to recurrence after 12 years. The CSFP observed both in the events and the improvement with nicorandil suggested that microvascular spasm played an important role in this case. CSFP is not uncommon in patients with Takotsubo cardiomyopathy and assessment of coronary flow with the TIMI frame count is easy; however, little attention has so far been paid to this phenomenon. Further investigations and the accumulation of more cases with the TIMI frame-counting method could therefore help to elucidate the role of microvascular constriction in Takotsubo cardiomyopathy.

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